

DECLARATION

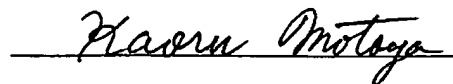
I, Dr. Kaoru MOTOYA, a national of Japan, 6th floor, Shinjukugyoen Bldg., 3-10, Shinjuku 2-chome, Shinjuku-ku, Tokyo 160-022, JAPAN do hereby solemnly and sincerely declare :

(1) THAT I am well acquainted with the Japanese language and English language, and

(2) THAT the attached is a full, true and faithful translation into the English language checked by me of true copy of Japanese Patent Application, No. 2004-024373 filed in the Japanese Patent Office on January 30, 2004.

And, I, Dr. Kaoru MOTOYA, being sworn state that the fact set forth above are true.

Signed this 4th day of February, 2009

A handwritten signature in cursive script, reading "Kaoru Motoya", is written over a horizontal line.

Dr. Kaoru MOTOYA

[Name of the Document] Claims

What is claimed is:

1. A method of catalytic reductive reaction using a micro-reactor, characterized in that:

said method of catalytic reductive reaction uses a micro-reactor with a metal catalyst or a metal complex catalyst as a solid phase supported on the inner wall of the channel,

a solution dissolving a reactant to be reduced as a liquid phase and hydrogen as a gas phase are flown through said channel in pipe flow state, and

three phase catalytic reductive reaction of solid – liquid – gas phases is conducted in which the reaction of said solution and said gas is accelerated by said metal catalyst or said metal complex catalyst.

2. The method of catalytic reductive reaction using a micro-reactor as set forth in claim 1, characterized in that said metal catalyst or a metal complex catalyst is incorporated in a polymer.

3. The method of catalytic reductive reaction using a micro-reactor as set forth in claim 1 or 2, characterized in that said metal catalyst incorporated in a polymer is palladium.

4. The method of catalytic reductive reaction using a micro-reactor as set forth in claim 1 or 2, characterized in that said metal complex catalyst incorporated in a polymer is a palladium complex catalyst.

5. The method of catalytic reductive reaction using a micro-reactor as set forth in claim 1 or 2, characterized in that said metal catalyst incorporated in a polymer is either one of chromium, manganese, iron, cobalt, nickel, copper, molybdenum, ruthenium, rhodium, tungsten, osmium, iridium, and palladium.

6. The method of catalytic reductive reaction using a micro-reactor as set forth in claim 1 or 2, characterized in that said metal complex catalyst incorporated in a polymer is a metal complex catalyst of either one of chromium, manganese, iron, cobalt, nickel, copper, molybdenum, ruthenium, rhodium, tungsten, osmium, and iridium.

[Name of the Document] SPECIFICATION

[Name of the Invention] METHOD OF CATALYTIC REDUCTIVE REACTION USING MICRO-REACTOR

[Technical Field]

[0001] The present invention relates to a method of catalytic reductive reaction using a micro-reactor.

[Background Art]

[0002] The catalytic hydrogenation reaction using a heterogeneous catalyst, so-called catalytic reductive reaction is one of the most important processes in chemical industry, and is widely utilized for hydrogenation of aromatic nitro compounds and unsaturated bonds or de-benzylolation reaction by hydrogenation, but there are often deterioration of yield and slow-down of reaction proceedings. Since these problems are solved by increasing the contact area between each phase, the catalytic surface (solid phase) – solution (liquid phase) – hydrogen gas (gas phase) (hereinafter, to be called a solid – liquid – gas phase reaction or three phase catalytic reduction reaction), such techniques have been tried as vigorous stirring or blowing in hydrogen gas as fine bubbles.

In the catalytic hydrogenation reaction in an ordinary reactor (hereinafter, properly called a flask reaction), ignition or explosion may be possible since hydrogen gas, solvent vapor, and highly active metal catalysts co-exist in the system.

[0003] On the other hand, organic syntheses using a micro-reactor have been rapidly developing. A micro-reactor is a generic term for a micro-reactor having micro-channels of the size of several to several hundred μm in an inactive material such as glass. Since a micro-reactor is small, strict temperature control is easily possible. Therefore, synthetic reactions using a micro-reactor have such merits as (1) high reaction efficiency on interfaces, (2) efficient mixing by molecular diffusion, and (3) easy temperature control, owing to large surface area per unit volume.

Thus, since synthetic reactions using a micro-reactor are

faster in reaction time than those using ordinary reactors, and use a minute amount of reactants, the cost is low and they have been drawing attention as the reactors to develop novel compounds and medicines.

[0004] In Non-patent Reference 1 in the list shown below, a hydrogenation reaction using a micro-reactor is described, which is a two-phase reaction of gas – solid with a catalyst immobilized on the inner wall of a micro-channel.

[0005] As the methods to pass liquid and gas as reactants through the micro-channels of a micro-reactor, a slug flow and a pipe flow are known.

Fig. 6 is a cross-sectional view diagrammatically illustrating (a) slug flow and (b) pipe flow in a conventional micro-channel. As is shown in Fig. 6(a), a slug flow is the state of liquid 52 and gas 53 alternatively passing through a micro-channel 51 provided on a glass substrate. Also, as is shown in Fig. 6(b), as a pipe flow, gas 53 passes in the center part of a micro-channel 51, and liquid 52 passes between the gas 53 and the inner wall 51a of a micro-channel. Which type, a slug or a pipe flow, the fluid in a micro-channel takes can be controlled by adjusting the flow rates of liquid 52 and gas 53 passing through a micro-channel 51.

[0006] The reactions by a slug flow in a micro-channel are described in the Non-patent References listed below. Non-patent Reference 2 describes fluorination reaction by a two phase reaction with gas – liquid phases.

[0007] The reactions by a pipe flow in a micro-channel are mentioned in the Non-patent References listed below. Non-patent Reference 3 describes fluorination reaction by two phase system reaction with gas – liquid phases. Non-patent Reference 4 describes hydrogenation reaction by pseudo-pipe flow in which a catalyst carried on a solid is packed in a micro-channel.

[0008]

[Non-patent Reference 1] R.S. Besser, and two others, Chem. Eng. Sci., Vol.58, p.19 (2003)

[Non-patent Reference 2] K. Jahnisch, et al., J. Fluorine

Chem., Vol. 105, p.117 (2000)

[Non-patent Reference 3] R. D. Chambers and R. C. H. Spink,
Chem. Commun. 883 (1999)

[Non-patent Reference 4] M. W. Losey, and two others, Chem.
Ind. Eng. Chem. Res., Vol.40, p.2555 (2001)

[Non-patent Reference 5] R. Akiyama and S. Kobayashi, J. Am.
Chem. Soc., Vol.125, pp.3412 – 3413 (2003)

[Disclosure of the Invention]

[Problems to be Solved by the Invention]

[0009] However, three phase catalytic reductive reactions of solid – liquid – gas phases using a heterogeneous catalyst have never so far been effectively realized by a micro-reactor.

[0010] In view of the problems mentioned above, it is an object of the present invention to provide a method of catalytic reductive reaction using a micro-reactor capable of conducting three phase catalytic reductive reaction of solid – liquid – gas phases in short time at high yield.

[Means to Solve Problems]

[0011] In order to attain the above-mentioned object, a method of catalytic reductive reaction of the present invention is a method of catalytic reductive reaction using a micro-reactor with a metal or a metal complex catalyst supported as a solid phase on the inner wall of a channel, characterized to flow the solution as a liquid phase in which the reactants to be reduced are dissolved and hydrogen as a gas phase through a channel in a pipe flow state, thereby to conduct the reaction of a solution and a gas accelerated by a metal catalyst or a metal complex catalyst in the three phase catalytic reaction of solid – liquid – gas phases. According to the above-described aspect, hydrogenation and hydrogenative decomposition reactions by the three phase catalytic reductive reaction of the reactants to be reduced can be conducted in a short time at high yield.

[0012] In the above-described aspect, the metal catalyst or the metal complex catalyst is preferably incorporated in a polymer. The metal

catalyst is preferably palladium. The metal complex catalyst is preferably a palladium complex catalyst.

The metal catalyst incorporated in a polymer is preferably either chromium, manganese, iron, cobalt, nickel, copper, molybdenum, ruthenium, rhodium, tungsten, osmium, iridium, or platinum.

The metal complex catalyst incorporated in a polymer is preferably a metal complex catalyst of either chromium, manganese, iron, cobalt, nickel, copper, molybdenum, ruthenium, rhodium, tungsten, osmium, iridium, or platinum.

By these catalysts, three phase catalytic reductive reaction can be conducted in short time by supporting a catalyst on the inner wall of a micro-channel of a micro-reactor. Further, since such complicated operation as separation of products and a catalyst and recovery of a catalyst is unnecessary, continuous operation of long time is possible.

[Effect of the Invention]

[0013] According to a method of catalytic reductive reaction using a micro-reactor of the present invention, such reactions as hydrogenation of reactants to be reduced can be conducted in a short time at high yield.

Also in the method of catalytic reductive reaction using a micro-reactor of the present invention, since such feed materials as reactants to be reduced and gases and the electric power or others required for their supply or agitation are quite little in quantities, it is at lower cost compared with conventional reactions using a reactor. Therefore, the three phase catalytic reductive reaction necessary in search for medicines or fine chemicals can be conducted at low cost.

[Best Modes for Carrying Out the Invention]

[0014] The present invention will be explained in detail below based on the forms of implementations illustrated in the figures.

Fig. 1 diagrammatically illustrates the makeup of a micro-reactor used in the embodiments of the present invention, and

(a) is a plan view and (b) is a partial cross-sectional view along a line Y - Y. A micro-reactor 1 is provided with substrates 2 and 3 made of an inactive material such as glass, micro-channels 4 provided snakingly on the substrate 2, a catalyst 5 immobilized, that is, supported on the surface of the micro-channel 4, a solution 7 in which reactants to be reduced are dissolved supplied via a liquid-feeding pump 6, a hydrogen gas cylinder 9a supplying hydrogen 9 supplied via a gas valve 8, and a vessel for recovery 10.

[0015] The micro-channel 4 is made with its cross-section carved in oblong or semi-circular shape by grinding with a tool such as an end mill or by etching with a mask. As is shown in Fig. 1(b), the substrate 2 on which the micro-channel 4 is provided is tightly fixed with a substrate 3 of the same size on which a micro-channel is not carved face to face so that the solution 7 and hydrogen 9 do not leach. Here, the substrate 2 on which a micro-channel 4 is carved and the substrate 3 facing thereto may be of a material not corrosive by reactants to be reduced or organic solvents, and may be of such a material as resins and metals in addition to glass.

[0016] The solution 7 is connected with the liquid-feeding pump 6 and Teflon (registered trademark) tube, and its supply rate is controlled by a flow rate adjuster using a syringe pump or others (not shown). Similarly, the hydrogen gas cylinder 9a is connected with the gas valve 8 and Teflon (registered trademark) tube, and its supply rate is controlled by a flow rate adjuster using a mass flow controller or others (not shown). The solution 7 and hydrogen 9 are combined at an inlet part 4a of the micro-channel. The vessel for recovery 10 is connected to an outlet part 4b of the micro-channel with Teflon (registered trademark) tube or others.

[0017] Fig. 2 is a cross-sectional view illustrating the states of a solution and hydrogen passing through a micro-channel of the present invention. As shown, hydrogen 14 passing through a micro-channel passes through a center part of the micro-channel 4. The solution 12 passing through a micro-channel passes between hydrogen 14 passes through a micro-channel and a catalyst supported on an inner wall 4c of the micro-channel in a so-called pipe flow state, from the inlet part

4a to the outlet part 4b. In this case, the flow rates of the solution 7 and hydrogen 9 are controlled to be in the above-mentioned pipe flow state by the flow rate adjusters not shown of the solution 7 and hydrogen 9.

[0018] In order to conduct solid - liquid - gas phase reaction using such a micro-reactor 1, a liquid reactant 7 from a liquid-feeding pump 6 and hydrogen 9 from a gas valve 8 are injected into a micro-channel 4 so to be in a pipe flow. While passing through the micro-channel 4, the reactant solution 12 and hydrogen 14 passing through the micro-channel are reacted by the action of a catalyst 5 supported on its inner wall 4c. The reaction mixture containing the object formed by reaction is collected into a vessel for recovery 10, and taken out upon necessity.

[0019] As the solid catalyst 5 used for the solid - liquid - gas phase reaction, a metal or a metal complex catalyst of either of Chromium (Cr), manganese (Mn), iron (Fe), cobalt (Co), nickel (Ni), copper (Cu), molybdenum (Mo), ruthenium (Ru), rhodium (Rh), tungsten (W), osmium (Os), iridium (Ir), or platinum (Pt) may be used.

[0020] Also, the catalyst 5 is preferably a polymer-inclusion catalyst (hereinafter to be called a PI catalyst) with the above-mentioned metal catalyst or metal complex catalyst immobilized in a polymer (Refer to the Non-Patent Reference 5.).

In order to firmly fix the PI catalyst 5 not to dissociate from the inner wall 4c of the micro-channel, it is preferred to immobilize, that is, to support by a covalent bond. For that, in case that the inner wall 4c of the micro-channel is glass, one end of a spacer 4d of the PI catalyst 5 mentioned below is modified with a trialkoxysilane structure, and bonded to a silanol group on the glass surface. Also, the other end of the spacer 4d can be bonded directly to, for example, an epoxy group on the polymer surface of the PI catalyst 5 by modifying it with a functional group such as amino acid group and others.

Also, in case that the inner wall 4c of the micro-channel is a resin, bonding is similarly possible to the above-mentioned epoxy group by modifying the resin surface with a functional group such as

amino acid group and others.

Since thereby the PI catalyst can be firmly supported on the inner wall 4c of a micro-channel, it does not dissociate from the inner wall 4c of a micro-channel, and can be used repeatedly.

[0021] Explanation is next made of an example of the method to support the PI catalyst 5.

Fig. 3 is a view diagrammatically illustrating the reaction to support a PI catalyst 5 in a micro-channel 4. As is illustrated, the catalyst is micro-encapsulated by dissolving a polymer in an appropriate solvent and further adding a substance containing the catalyst (See Fig. 3(a)). In said micro-encapsulated catalyst 5a, the metal or the metal complex is present not only inside the capsule but also on or near the surface.

Next, it is bonded to a glass surface 20 modified with a spacer having an amino group by passing the solution containing the micro-encapsulated catalyst 5 through a micro-channel, and heating (See Fig. 3(b)). Fig. 3(c) diagrammatically illustrates the inner wall of a micro-channel on which is supported the thus obtained PI catalyst 5, and 4d illustrates the spacer of the surface group of a micro-channel and the catalyst.

[0022] According to the method of three phase catalytic reductive reaction of the present invention, hydrogenation reaction can be conducted in short time by three phase catalytic reaction in so-called pipe flow state in which the solution 7 containing reactants to be reduced is flown contacting the inner wall 4c of the micro-channel on which the catalyst is supported, and hydrogen 9 flows at the center part of the micro-channel 4, that is, in a so-called pipe flow state to enable a three phase catalytic reaction in short time. In this case, since a metal catalyst 5 is supported on the micro-channel inner wall 4c, the recovery and regeneration work of, for example, valuable palladium catalyst is unnecessary, and further since it is the reaction in a micro-reactor 1, the amounts to be used of the reactants, solvents, and hydrogen 9 used for the reaction are so remarkably decreased that the cost is reduced.

Since also the scale up of a reactor apparatus is easy only by

arranging a number of micro-reactors 1 in parallel, the desired products can be obtained easily, quickly, and in the necessary amount, the feed-stock consumption, required time and space are low, and the products can be obtained in such a pure form that separation and refining are not necessary.

Therefore, according to the method of three phase catalytic reductive reaction of the present invention, it is the reaction method quite suitable to development of medicine and its manufacturing process. It is also preferred for green chemistry (environment-oriented chemistry).

[Example 1]

[0023] Explanation is next made of the examples of the present invention.

Using a micro-reactor 1 of Fig. 1, hydrogenation of benzalacetone as a substance to be reduced was conducted. As the micro-reactor, a glass plate 2 of size 3 cm X 7 cm having a micro-channel 4 of length 45 cm was used. The cross-sectional shape of the micro-channel 4 was 200 μ m wide and 100 μ m deep semi-circular. On the inner wall 4c of the micro-channel was immobilized polymer-inclusion palladium (hereinafter to be called PI palladium) 5 containing palladium fixed on polymer (See Fig. 3 (c)).

[0024] Into a micro-channel 4, THF (tetrahydrofuran) solution 7 of benzalacetone as a substance to be reduced (concentration 0.1 mole %/1000 cm^3) and hydrogen gas were supplied at flow rates 0.1 cm^3/hour and 1 $\text{cm}^3/\text{minute}$, respectively, the substance to be reduced and hydrogen 9 were passed through the micro-channel 4 in pipe flow state, thereby hydrogenation reaction of benzalacetone was conducted. The reaction was conducted at room temperature.

[0025] Next, the reaction product was analyzed by NMR using proton (nuclear magnetic resonance apparatus, hereinafter to be called ^1H -NMR).

Fig.4 is a view illustrating the reaction products from hydrogenation reaction of benzalacetone of Example 1. As is obvious from the figure, 4-phenyl-2-butanone and 4-phenyl-2-butanol were

obtained by hydrogenation of benzalacetone within five minutes as reaction time at the yield of 97% and 3 %, respectively.

The hydrogenation reaction time of Example 1 was calculated as about five minutes from the whole volume of the micro-channel 4 and the volume flow rate of liquid phase, and its observed value was two minutes. This value of reaction time is about 1/30 compared with about one hour as the ordinary flask reaction.

[Example 2]

[0026] As Example 2, hydrogenation reaction was conducted under the same condition as Example 1 for THF diluted solution concentration of the substance to be reduced, its flow rate, and hydrogen 9 flow rate, using cyclohexen-2-one as the substance to be reduced. The reaction time was within five minutes. The reaction product was analyzed by ^1H -NMR. Fig. 5 is a view illustrating the yields of hydrogenation reaction of Example 2. As is obvious from the figure, the analytical result of the reaction product by ^1H -NMR showed almost complete hydrogenation of cyclohexen-2-one, and cyclohexanone was obtained at about 100 % yield.

[Example 3]

[0027] As Example 3, hydrogenation reaction was conducted under the same condition as Example 1 for THF diluted solution concentration of the substance to be reduced, its flow rate, and hydrogen 9 flow rate, using 2,4-diphenyl-4-methyl-1-pentene as the substance to be reduced. The reaction time was within five minutes. The analytical result of the reaction product by ^1H -NMR showed almost complete hydrogenation of 2,4-diphenyl-4-methyl-1-pentene, and 2,4-diphenyl-2-methylpentane was obtained at about 100 % yield (See Fig. 5.).

[Example 4]

[0028] As Example 4, hydrogenation reaction was conducted under the same condition as Example 1 for THF diluted solution concentration of the substance to be reduced, its flow rate, and

hydrogen 9 flow rate, using 1,4-diphenyl-1,3-butadiene as the substance to be reduced. The reaction time was within five minutes. The analytical result of the reaction product by ^1H -NMR showed almost complete hydrogenation of 1,4-diphenyl-1,3-butadiene, and 1,4-diphenylbutane was obtained at about 100 % yield (See Fig. 5 6.).

[Example 5]

[0029] As Example 5, hydrogenation reaction was conducted under the same condition as Example 1 for THF diluted solution concentration of the substance to be reduced, its flow rate, and hydrogen 9 flow rate, using 1,2-diphenylacetylene as the substance to be reduced. The reaction time was within five minutes. The analytical result of the reaction product by ^1H -NMR showed almost complete hydrogenation of 1,2-diphenylacetylene, and 1,2-diphenylethane was obtained at about 100 % yield (See Fig. 5.).

[Example 6]

[0030] As Example 6, hydrogenation reaction was conducted under the same condition as Example 1 for THF diluted solution concentration of the substance to be reduced, its flow rate, and hydrogen 9 flow rate, using 3-phenyl-2-propin-1-ol as the substance to be reduced. The reaction time was within five minutes. The analytical result of the reaction product by ^1H -NMR showed almost complete hydrogenation of 3-phenyl-2-propin-1-ol, and 3-phenyl-1-propanol was obtained at about 100 % yield (See Fig. 5.).

[Example 7]

[0031] As Example 7, hydrogenation reaction was conducted under the same condition as Example 1 for THF diluted solution concentration of the substance to be reduced, its flow rate, and hydrogen 9 flow rate, using 1-phenylcyclohexene as the substance to be reduced. The reaction time was within five minutes. The analytical result of the reaction product by ^1H -NMR showed almost complete hydrogenation of 1-phenylcyclohexene, and phenylcyclohexane was obtained at 99 % yield (See Fig. 5.).

[0032]

The present invention is not limited to the above-described examples, but rather various modifications are possible within the range of the invention as set forth in the claims, and needless to say these are also included in the range of the present invention.

[Brief Description of the Drawings]

[0033]

Fig.1 diagrammatically illustrates the makeup of a micro-reactor used in the embodiments of the present invention, and (a) is a plan view and (b) is a cross-sectional view along a line Y – Y.

Fig. 2 is a cross-sectional view illustrating the states of a solution and hydrogen passing through a micro-channel of the micro-reactor used in the present invention.

Fig. 3 is a view diagrammatically illustrating the reaction to support a PI catalyst in a micro-channel.

Fig. 4 is a view illustrating the reaction products from hydrogenation reaction of benzalacetone of Example 1.

Fig. 5 is a view illustrating the yields of hydrogenation reaction of Examples 2 – 7.

Fig. 6 is a cross-sectional view diagrammatically illustrating (a) a slug flow and (b) a pipe flow in a conventional micro-channel.

[Explanation of Marks and Symbols]

[0034]

- 1: Microreactor
- 2, 3: Substrate
- 4: Microchannel
- 4a: Inlet Part of Microchannel
- 4b: Outlet Part of Microchannel
- 4c: Inner Wall of Microchannel
- 4d: Surface Group of Microchannel
- 5: Catalyst supported on Microchannel Surface
- 5a: Microcapselized Catalyst
- 6: Feed Pump

- 7: Solution
- 8: Gas Valve
- 9: Hydrogen
- 9a: Hydrogen Cylinder
- 10: Recovery Vessel
- 12: Reactant Solution passing Microchannel
- 14: Hydrogen passing Microchannel

[Name of the Document] Abstract

[Abstract]

[Problems] A method of catalytic reductive reaction is provided which can conduct a solid · liquid · gas 3 phase catalytic reductive reaction in short time at high yield using a microreactor.

[Means to Solve Problems] This is a method of catalytic reductive reaction using a microreactor 1 of which an inner wall 4c of a channel 4 has a metal catalyst 5 or a metal complex catalyst 5 supported thereon. A solution 7 as a liquid phase containing a reactant to be reduced dissolved therein and hydrogen 9 as a gas phase are flown in the channel 4 in a pipe flow state, and a solid · liquid · gas 3 phase catalytic reductive reaction is conducted to accelerate reaction of the solution 7 and the gas 9 with a metal catalyst 5 or a metal complex catalyst 5. The metal catalyst 5 or the metal complex catalyst 5 is incorporated in a polymer. Hydrogenation reaction of a reactant to be reduced by 3 phase catalytic reductive reaction can be conducted in short time at high yield. For hydrogenation reaction of unsaturated organics has high reaction rate and yield if palladium catalyst is used.

[Selected Figure] Fig. 1